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Using Biomarkers to Inform Cumulative Risk Assessment

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Abbreviations:

ADHD	Attention Deficit Hyperactivity Disorder
ADs	Asthma and related allergic diseases
CDC	Centers for Disease Control and Prevention (CDC)
EPA	United States Environmental Protection Agency (EPA)
IgE	immunoglobulin E
OCs	organochlorine pesticides
OP	Organophosphate pesticides
PCBs	Polychlorinated Biphenyls
POPs	Persistent Organic Pollutants
RAST	Radioallergoabsorbent Test
TCPy	3,5,6-trichloro-2-pyridinol (TCPy)
VOCs	volatile organic compounds (VOCs)

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ABSTRACT

In this work we explore the relationship between environmental exposures and health outcomes as mitigated by differential susceptibility in individuals or populations. Specifically, we address the question "Can biomarkers enable us to understand and quantify better the population burden of disease and health effects attributable to environmental exposures?" We use a case-study approach to develop the thesis that biomarkers offer a pathway to disaggregation of health effects into specific, if multiple, risk factors. In particular, we offer the point of view that a series or array of biomarkers, including biomarkers of exposure, biomarkers of susceptibility, and biomarkers of effect used in concert offer the best means by which to effect this disaggregation. We commence our discussion by developing the characteristics of an ideal biomarker, and then give some examples of commonly used biomarkers to show the strengths and weaknesses of current usage. We propose a research agenda suggesting simultaneous collection of multiple biomarkers and evaluation of multiple effects in an effort to develop fuller understanding of the exposure-to-dose continuum. This is followed by more detailed case-study assessment outlining the state-of-the-science for three different disease outcomes- asthma in children, neurobehavioral effects associated with heavy metal exposure, and an ecosystem approach focusing on persistent organic pollutants. We complete our work with some recommendations regarding the future use of biomarkers and areas for continued development.

Using Biomarkers to Inform Cumulative Risk Assessment

INTRODUCTION

The United States Environmental Protection Agency (EPA) defines cumulative risk as the combined risks from aggregate exposure to multiple stressors (USEPA 2003c), and cumulative risk assessment as an analysis, characterization, and possible quantification of these risks. In this and companion papers (Callahan and Sexton. 2006), we explore approaches for assessing the effects of stressors from multiple sources (Menzie et al. 2006), the effects of differential vulnerability in populations and individuals (deFur et al. 2006), and the effects associated with differential exposure (Sexton and Hattis 2006).

This paper provides an evaluation of whether and how biomonitoring data can inform cumulative risk assessment. We examined the potential for human and ecosystem biomarkers to help us understand cumulative health risks from the interactions between environmental exposures and host susceptibility factors. We used case studies to address the question:

- Can biomarkers enable us to understand and quantify better the population burden of disease and health effects attributable to environmental exposures?"

Further, we present examples from the current literature on the availability and uses of biomarkers to explore two other questions:

- Under what circumstances can biomarkers be used to disaggregate disease burden into specific risk factors? For example, when and how can biomarkers be linked to specific diseases and can a specific biomarker or set of biomarkers be useful for mapping disease to exposure?

- When and how can biomarkers be used to infer the source and magnitude of exposure among a set of competing sources and pathways?

The latter question centers on the inverse problem of disaggregating cumulative exposures into their component parts. This is a difficult problem that is only now receiving attention in the scientific community.

Biomarkers may offer improved understanding of the pathway between the causative agents, as indicated by exposure measures, and the health outcome. There are many challenges and limitations. What are the public health implications of widespread low-level population exposures that can now be inferred from biological or ecological measurements? Disaggregating the health effects and understanding the health risk from these exposures will require new perspectives on the environmental health paradigm. Ideally, biomonitoring will become a foundation of an environmental public health tracking system that includes identification of environmental sources, exposures, and related population health outcomes (Barr et al. 2005). Combining biomonitoring results with population health surveillance offers opportunities for understanding the relationship between cumulative exposures and population, community, and individual risk.

BIOMARKERS AS A POSSIBLE BASIS FOR ENVIRONMENTAL REGULATION

Medical surveillance studies of disease burdens provide insight on cumulative impacts from multiple risk factors, but do not provide a framework to attribute risk factors to disease. This attribution is necessary for regulation. The problem is finding a measurable basis for regulation of disease-causing agents that provides a quantitative or qualitative link or links

between disease and its causative agent(s) in the environment. Biomarkers in human and ecological populations may provide this basis.

We define biomarkers as measures reflecting an interaction between a biological system and a chemical, biological, or physical environmental agent. The focus is on chemical agents although the methods developed are applicable in other areas. The literature usually considers three classes of biomarkers (NRC 1987; WHO 1993): *Biomarkers of exposure; Biomarkers of effect; and, Biomarkers of susceptibility.* The first two link exposures with health outcomes and can provide the basis for linking biological effect and exposure to environmental contamination. The third refers to a modifier that influences the magnitude of the effect given a fixed magnitude of the driver. All three types may be used to identify vulnerable individuals or populations.

Characteristics of an Ideal Biomarker

We used the characteristics of an ideal biomarker to evaluate the current state of research, guide the use of specific biomarkers, and to suggest future research. The literature on the criteria for defining, developing, and validating an ideal biomarker (Groopman and Kensler 2005; Metcalf and Orloff 2004; Schulte and Mazzuckelli 1991; WHO 1993) suggests eight criteria for evaluating a biomarker's usefulness in cumulative risk assessment. Ideal biomarkers would:

Be Persistent - have a long half-life;

Be Easily Collected - collected using non-invasive procedures that present only minor procedural difficulties in collection, transport, storage, and analysis;

Be Linked to Disease - display exposure, indicate effect, and establish a link between them;

Have a Large Sample - to examine the distribution of the biomarker in the population and to establish links between the biomarker and effect;

Have Broad Spatial Distribution and Temporal Occurrence - a complete spatial and temporal understanding of the exposure/health outcome distribution;

Have Sensitivity - sufficiently sensitive to give information on differences in populations from different regions and over time scales of interest, e.g., seasonal or long-term, secular trends.

Favor Measurement of Parent Compounds over Metabolites - The measurement of parent compound gives a direct and unambiguous measure of exposure to the contaminant of interest.

Table 1 presents an outline of considerations for biomarkers including a hypothetical biomarker that illustrates the criteria. Table 1 shows that even commonly used biomarkers are far from ideal, but that combinations of biomarkers for the same compound may give complementary information.

AN ARRAY OF BIOMARKERS IN CUMULATIVE RISK ASSESSMENT

While a biomarker of exposure may be appropriate in assessing exposures over one time scale, health outcomes, and thus risk, may be associated with time scales markedly different from those being assessed. Further, exposure to a specific compound – a biomarker of exposure – may be insufficient to assess effects; a biomarker of effect may be needed. Finally, if one is concerned about large populations and the health impact they are likely to experience, then one must be concerned about differential susceptibility in the population; a biomarker of susceptibility is needed. Thus the “ideal” biomarker may not exist.

Application of Array Concept - Organophosphate Pesticides

It may be possible to approach the ideal biomarker functionally by applying an array of biomarkers, each of which provides some of the ideal characteristics. For example, organophosphate (OP) pesticides have widely varying chemical structures but share a common toxic mechanism of action: acetylcholinesterase inhibition. While exposure to organophosphate pesticides has been linked to neurological effects, this primary mechanism of action is actually a short-term, or early, effect (Figure 1.)

Biomarkers of exposure to these compounds exist. Dialkyl phosphates (Barr et al. 2004) and organophosphate-specific (or near-specific) biomarkers such as 3,5,6-trichloro-2-pyridinol (TCPy) (MacIntosh et al. 1999) offer two approaches to assessing organophosphate pesticide exposure. The non-specific biomarker for organophosphate pesticides, dialkyl phosphates, may offer insight into the general exposure to these pesticides, and a pathway to cumulative risk assessment, while the OP-specific biomarker gives insight into exposure to specific members of this class, e.g., chlorpyrifos (and chlorpyrifos-methyl) and some insight into metabolic processes. Measurement of the compound-specific biomarker, e.g., TCPy, can give information only on exposure to the compounds from which it is derived. Further, interpretation is complicated due to levels of TCPy in exposure media. While the dialkyl phosphates measure gives information on all compounds of this general class, each member of the organophosphate class has different inhibition characteristics. The measure of the non-specific metabolites does not give information on the specific compound from which they came, reducing their utility.

Measuring acetylcholinesterase inhibition, a biomarker of effect, directly may add some insight into susceptibility but it provides no information on the cause of inhibition. This

discussion suggests that the *simultaneous* collection of all three biomarkers is likely to lead to substantially more information than collection of the individual markers alone.

A FRAMEWORK FOR APPLYING AN ARRAY OF BIOMARKERS AND OTHER METRICS

The framework presented in Figure 1 provides the conceptual basis for considering an array of biomonitoring data and other health metrics in assessment of cumulative exposure and risk. The receptor may be a human being, an individual organism, a population, a community, or an ecosystem. Multiple sources result in a range of environmental conditions with a range of temporal and spatial exposures to multiple stressors (See (Sexton and Hattis 2006).) These multiple exposures at varying times may be required to induce any one outcome.

The framework uses:

- Biomarkers of susceptibility to characterize the receptor (e.g. information on genetics, developmental or life stage, and health status) (See (deFur et al. 2006));
- Biomarkers of effect to characterize the potential for adverse outcomes (e.g. may range in scale from early effects detectable at a molecular level to manifestations of the full disease state); and
- Biomarkers of exposure to characterize direct impact of stressors on the receptor (See (Menzie et al. 2006).) Linking these internal markers of exposure to associated chemical, biological, physical, or psychosocial stressors will often require consideration of

additional information on conditions of the environment and interaction of the receptor with the environment.

Applying the Framework

Multiple Sources

Even for a specific contaminant, there is the potential for multiple sources and pathways of exposure. For example, in the case of organophosphate pesticides, a receptor can be exposed through various sources through ingestion of agricultural crops or direct contact from local application for pest control. Each of these sources results in environmental contamination, but the movement through the environment to produce the resulting exposure is substantially different. One may attempt to monitor the food supply, house dust, soil, and air concentrations (the exposure) and infer dose to the receptor through a modeling process that estimates intake to the body based on the amount of specific compound found in each of the media. However, such calculations are difficult and results depend upon the model selected.

Factors Influencing Effects

Three factors of interest influence the effects observed on the receptor: genetic susceptibility, developmental stage, and health status (Figure 1). Genetic susceptibility, for example through differential metabolism of OP pesticides among various individuals, communities, or populations may result in different effects for a given exposure. Developmental stage is an important determinant of the effects of exposure. Perhaps the most visible case of such effects occurred in the so-called “thalidomide babies” born to mothers who took this drug in the early 1960s. Developmental stage was critical; those who were exposed to thalidomide at a

particular stage of gestation suffered from the exposures while others exposed later in gestation, or not at all, did not experienced any such effects. On the effects side (the right part of Figure 1) there are various levels of outcomes ranging from often sub-clinical "early effects," through altered structure and function, leading to a measured adverse outcome. It is important to note that a dose from a single chemical may lead to multiple early effects, altered structure and functions, and outcomes. For example, exposure to lead may lead to cognitive defects, neurological effects, and altered blood pressure status. Thus, one progresses from a multifactorial source/exposure/dose relationship, modified by receptor status with respect to development, susceptibility, and health, to multifactorial outcomes.

Health Status of the Receptor

Health status of the receptor can also affect the outcome of a given exposure. Those with compromised immune systems due to disease status, or those with, for example, little excess pulmonary capacity, may be more adversely affected to a given exposure than those not suffering from these conditions. Similarly, an ecosystem under stress from, say, ozone exposure, may respond differently to herbicides than a healthier ecosystem (Menzie et al. 2006, Sexton and Hattis 2006). The key question becomes: How do we think about the appropriate array of biomarkers needed to assess fully the outcomes of interest for the specific receptor?

SETTING A RESEARCH AGENDA

The review of biomarker data indicates that there probably is no single, ideal biomarker (e.g., Table 1), and the discussion of using an array of biomarkers to assess the cumulative effects of

various contaminants, poses various established uncertainties (e.g., a full suite of biomarkers – exposure, susceptibility, and effect) may not exist for a specific compound. However, we believe that an integration of the characteristics of an ideal biomarker with existing knowledge of the specific difficulties surrounding a specific outcome of concern can offer research recommendations. This is a simple matrix that matches a set of evaluation criteria (the criteria that define an ideal biomarker) to the current state of knowledge (an array of existing biomarkers and other health criteria). One can use that knowledge to fill the matrix and specify the uncertainties associated within each match-up. Figure 1 present the essentials of the matrix. At a minimum, the questions addressed in each element should include:

- Does the biomarker have the desired criteria?
- Are there multiple sources that affect the biomarker?
- Is the biomarker indicative of genetic status?
- Is the biomarker indicative of developmental stage?
- Is the biomarker indicative of health status?
- Are there many potential outcomes (e.g., multiple early effects, altered structure and functions, and changed health status)?

The answers to these questions, informed by the ideal criteria, will produce a coherent research agenda vulnerable to prioritization.

BIOMARKERS AND DISEASE OUTCOMES - ILLUSTRATIVE CASE STUDIES

To this point, the focus has been on the exposure side, approaching biomarkers as a method of assessing exposure experienced by a receptor to some environmental contaminant. We now change the focus to outcome. A question is posed: *Can the presence of certain biomarkers in the receptor aid in evaluating the source of a particular health outcome?* Three cases studies are presented on disease outcomes of concern: asthma, neurobehavioral effects, and endocrine disruption. All are complex diseases with many different manifestations. All have multiple biomarkers including those of exposure, effect, and susceptibility that can be used singularly and in combination to assess the contaminant sources affecting the disease and the disease outcome. We propose to evaluate multiple biomarkers simultaneously, the main proposal advocated in this work. For one of these cases, asthma, the matrix in Table 2 is applied to assess the status of each associated biomarker relative to the ideal.

Asthma and Asthma Etiology Markers and Effects

Background

Asthma and related allergic diseases (ADs) are manifested by numerous environmentally related sources, and numerous potential outcomes. In the United States, recent surveys find a 16% prevalence of asthma among 14-year old children, with a 200% increase in the rate of asthma hospitalizations and a 100% increase in the rate of asthma mortality since the 1970s. The *atopic march* is the accepted natural history of ADs and refers to a sequence of early immunologic and later clinical responses that may appear in young children, persist over years, and may continue throughout one's lifetime (Kulig et. at., 1999). A series of biomarkers may

afford an improved understanding of the effects of various sources on the etiology of these related diseases. Examination of the contaminant sources thought to influence the course of the atopic march and the biological markers associated with this process is instructive in light of the concepts presented in this paper.

Sources and Exposures

There is much evidence to suggest that components of the early childhood indoor and outdoor environments are contributing to the increasing prevalence of ADs (Figure 2). Various air borne sources are associated with the etiology of ADs and the specific development of asthma. These include: photochemical and particulate air pollution (Andrae et al. 1988; Diaz-Sanchez et al. 1997; Lunn et al. 1970; Peterson and Saxon 1996; Ussetti et al. 1984; Ware et al. 1986); criteria air pollutants, diesel exhaust carbon particles, and pesticides that increase allergic sensitization (Behrendt et al. 1997; Emberlin 1995; Knox et al. 1997; MacIntosh et al. 1999; Rubbin et al. 1986; Ruffin et al. 1986); and, elevated airborne levels of particulate matter (PM), particularly fine aerosol ($PM_{2.5}$) (Dejmek et al. 1999; Neas et al. 1994; Norris et al. 1999; Romieu et al. 1996).

Individuals living in industrialized societies also tend to spend a larger fraction of time in indoor environments that have higher allergen and chemical burdens (Platts-Mills et al. 1996). There is some evidence that indoor exposure to volatile organic compounds (VOCs) can be related to asthmatic symptoms (Harving et al. 1991). Among infants exposed to environmental tobacco smoke, studies demonstrate that the risks of lower airway disease and recurrent wheezing are increased (Arshad and Hide 1992; Murray and Morrison 1990; Wahn and von Mutius 2001). Exposure to household endotoxin may also be important in the development of ADs. There is evidence that high levels of household endotoxin may mitigate the development

of ADs before disease onset, but may exacerbate the symptoms of ADs once developed (Gereda et al. 2001; Gereda et al. 2000; Park et al. 2001).

Biomarkers of Susceptibility, Exposure, and Effect

Several biological markers of nascent hypersensitivity exist (Figure 2). These include immunoglobulin E [IgE], Radioallergoabsorbent Test (RAST)-positivity, and T-helper type 2 [Th2] cytokine pattern predominance, indicative of imbalance in the development of the immune system in newborns and young children, and early clinical manifestations of ADs including early development of food allergies and atopic dermatitis manifested as skin rashes. Both genetic and environmental factors have been implicated (Miller 2001). One early marker for atopic immunoreactivity in infancy is the presence of IgE antibody to egg or cow's milk in serum. The first clinical manifestation of atopic immunoreactivity is, typically, atopic dermatitis, with the highest incidence during the first three months of life, followed by food allergy (Wahn and von Mutius 2001). Those who develop the early clinical manifestations including food allergies and atopic dermatitis, are at higher risk for persistent asthma (Martinez et al. 1995). Thus measure of these markers may be viewed as early indicators of altered structure or function (See Figure 2.)

The combination of the measurement of multiple biomarkers of susceptibility and effect coupled with better measures of exposure to multiple pollutants is likely to lead to a more complete understanding of the progression of ADs and the increased incidence and prevalence of asthma in modern, industrialized societies. Disaggregation of the effects is still problematic. Despite the presence of measures of early effect, few data have been collected that show the path

of causality from source, (e.g., criteria pollutants), through biomarker (e.g., Th2 cytokine path dominance), to the onset of asthma.

Neurobehavioral Endpoints

Background

Several neurobehavioral endpoints have been linked to environmental exposures. Some important known behavioral neurotoxins include mercury and lead. However, making specific chemical/exposure links is difficult because the causes of human disease are varied – resulting from a mixture of environmental, lifestyle, socio-economic, and genetic factors acting over the life time of the individual.

Examples of Neurobehaviorally Active Substances with Multiple Exposure Pathways (See Figure 3)

Mercury

Mercury is a neurotoxic substance that can produce a wide range of health effects depending on the amount and timing of exposure (Clarkson 1997; Ratcliffe et al. 1996; USEPA 1997). Mercury is a naturally occurring element found in the earth's crust but human activities contribute significantly (an estimated 70%) to the amount of mercury circulating in the environment (Kyerematen and Vesell 1991). Because of its persistence and the large and distributed number of sources, almost everyone will be exposed to low levels of mercury in air, water, or food (USEPA 1997).

Mercury is somewhat persistent in human tissues (USEPA 1997). This makes it feasible to assess human exposure using blood, hair, and urine. Concentrations of mercury in maternal blood, cord blood, and maternal hair have been used to asses the potential for developmental neurobehavioral endpoints, but there are significant inter-individual variability in the relationship among blood-to-hair, blood-to-intake, or hair-to-intake ratios (Bartell et al. 2000). In addition to hair and cord blood, other biomarkers are emerging. For example, mercury selectively alters porphyrin metabolism in kidney proximal tubule cells, leading to an altered urinary porphyrin excretion pattern (Woods 1996) thereby offering a biomarker of effect.

Lead

Lead is a naturally occurring heavy metal that is widely distributed in the Earth's crust and found in soil, surface water, ground water, and vegetation and animal tissues. The human body has no known biological need for lead, but once taken in by ingestion, inhalation, or dermal contact, lead behaves like calcium in the body and is stored mostly in the bones with a small fraction in the blood. The levels of lead in the blood reach equilibrium with bone levels, but this often take months, even years. Short term high or low rates of intake can disrupt this equilibrium (Chuang et al. 2001).

Exposures to lead occur in occupational and residential settings. Children and most adults in the US are more likely to experience chronic low-to-moderate-level lead exposure than acute, high-level exposure.

Among the most significant health problems associated with these levels of lead are neurological development problems. In adults and children, chronic lower/moderate-level lead exposure has been associated with learning deficiencies, memory problems, behavior problems,

attention deficit, problems with coordination, anemia, digestive disorders, renal dysfunction, abnormal reproductive function, and possible infertility (Needleman and Bellinger 1991).

The level of lead in the blood is most often used as the measure of the amount of lead in the body. However, blood lead only relates to the lead exposure within the past few months Currently available tests are subject to numerous limitations such as unreliability and lack of sensitivity for values below a few µg/dL in blood (See Table 1.) This limitation is significant because similar blood lead concentrations have recently been shown to induce irreversible neuropsychologic damage in children (Tong et al. 1998). Like mercury, lead persists in the body so that levels in blood, hair, and bone have served as biomarkers of lead exposure. Lead in teeth and bones can be measured with X-rays, but this test is not readily available (See Table 1.) One of the factors limiting the progress of lead epidemiology has been the absence of a biomarker of long-term exposure. Therefore, considerable effort has been devoted to developing methods for the *in vivo* measurement of lead deposited in bone.

Effects in Children

The causes of human disease have numerous causative factors that result from a mixture of environmental, lifestyle, socio-economic, and genetic factors acting over the life time of the individual. However, in most cases the environment will serve, in varying degrees, to influence the initiation, severity and/or progression of disease (SB702 2004). Children are particularly vulnerable to environmental disease because: their bodies are still developing, they are exposed to more contaminants on a body-weight adjusted basis, and behaviors such as crawling, putting objects in their mouths, and running that can increase their environmental exposures. Among the

most serious diseases confronting children in US are neurodevelopmental and behavioral disorders. The manifestation of these diverse effects may arise through exposures to these suites of compounds in that similar (and multiple) effects may be noted for exposure to diverse compounds in the environment.

We consider three effects seen in children that may have etiology rooted, at least in part, in environmental exposure: Developmental and Reproductive Disorders, Attention Deficit Hyperactivity Disorder, and Delinquency. Examination of these effects in conjunction with multiple sources may offer a fruitful pathway for further understanding (see Figure 3.)

Developmental and Reproductive Disorders- Although chemical exposure may be one of the most preventable causes of reproductive disease, the scope of this problem has not been well defined and there have been only limited attempts at concerted research efforts to use biomarkers to assess cumulative exposures for all substances linked to developmental disorders. So the question to consider is: Are the substances that are currently known to have effective biomarkers likely to be the ones that will be the dominant contributors to this disease endpoint?

There has been recent concern that a signature metabolic impairment or "biomarker" in autistic children strongly suggests that these children would be susceptible to the harmful effects of mercury and other toxic chemical exposures (Parker et al. 2004). To address this issue, the CDC conducted its own epidemiologic study and then convened a panel of the Institute of Medicine (IOM) of the National Academy of Sciences to review the issue independently. On May 17, 2004, the IOM published its final report on the possible link between thimerosal and autism and concluded that neither the mercury-based vaccine preservative thimerosal nor the measles-mumps-rubella (MMR) vaccine are associated with autism (IOM 2004). But these

findings remain controversial and biomarkers could play a role in further confirming or challenging this finding.

Attention Deficit Hyperactivity Disorder (ADHD)- The causes of ADHD are currently not known. It appears to involve both genetic and environmental components. Possible causes of ADHD include physical trauma to the brain, problems during pregnancy or delivery, genetic abnormalities, and differences in brain structure (NIMH 2005) in addition or in concert with environmental exposures. There is some evidence that environmental exposures can cause problems with behavior and attention similar to those seen in children with ADHD. However, there is little evidence that environmental exposures clearly cause ADHD. For example, many human studies demonstrate that children with elevated lead levels have problems with behavior, impulsivity, and concentration. Several individual case studies suggest that lead exposure may be linked with ADHD. But these studies do not clearly show that lead exposure causes ADHD. Similarly, several human studies suggest that children exposed to methylmercury have an increased risk of behavioral problems. However, this finding is controversial. Not all studies support this association (NRC 2000).

Delinquency- Lead exposure has been associated with increased risk for antisocial and delinquent behavior, and the effect follows a developmental course (Needleman et al. 1996). This association links elevated bone lead concentrations and the risk of being arrested for criminal behavior. The underlying causes for this association are not certain. One possibility is that lead interferes with impulse control and that people who have a harder time controlling impulses are more likely to engage in criminal behavior. Another possibility arises from lead's well-established impact on cognitive function and classroom performance.

Endocrine Disruptors – An Ecological Point of View

Background

Ecosystems may offer sentinel effects with respect to ultimate human outcomes and may offer an improved understanding of the relationship between multiple sources of numerous contaminants, and the myriad of effects they can produce. Certain contaminants, because of their environmental persistence and slow degradation, are dispersed widely in the environment. Ideally, a biomarker should discriminate among populations from various regions and account for this widespread dispersion. There is ample evidence of persistent organic pollutants (POPs), such as PCBs, in organisms from developed countries. There is also evidence of food chain accumulation from animals and contaminated media in remote ecosystems (Figure 4). Marine animals and fish are contaminated with PCBs, organochlorine (OC) pesticides, and heavy metals in the Canadian Arctic (Muir et al. 1990), while in a Himalayan snowpit, there are organic compounds indicative of petroleum residues such as automobile and diesel exhaust (Xie et al. 2000). In the Puget Sound and North Pacific Ocean Harbor, PCBs have been detected in seals, sockeye salmon, and albatross (Ross 2004). Anthropogenic chemicals may spread throughout the environment through ingestion of migrating prey (Ross 2004), direct uptake, the transport of volatile chemicals through the atmosphere, or the transport of ionic and polar compounds dissolved in water (Ross 2004).

Ecosystem Exposure to Multiple Contaminants

Environments are often subject to exposure from multiple contaminants. Ideally, suites of biomarkers could be used to identify the many chemicals present. In many field studies,

aquatic organisms have been exposed to a complex mixture of organochlorines, heavy metals, and other various contaminants (Kuzyk et al. 2003). Ecosystem contamination as a result of multiple chemicals affects a species differently than contamination by a single chemical. The effects of mixtures usually exceed those of the most active constituents alone (Faust et al. 2004). For example, in a study assessing the effects of cadmium and zinc on rainbow trout, an exposure to a mixture of the metals resulted in a greater biological response than from exposure to each individual metal (Lange 2002).

Contaminants affect the biota throughout an ecosystem in different ways and can elicit various effects, each of which may be detected by a biomarker. In one case, marine gastropods were exposed to multiple organotins such as tributyltin (TBT) and triphenyltin (TPT) and, as a result, the organisms suffered genotoxicity, inhibition of ATP synthesis, and inhibition of CYP enzymes (Fent 2004). The responses to the same contamination are often species-specific in organisms ranging from bacteria and green algae (Ma et al. 2004) to fish (Lemly 1997).

Effects of contamination are not only species-specific, but can vary according to specific chemical interactions as well. Timing and mode of exposure of pollutants, compound toxicity, and age of subjected organisms (Figure 6) are factors responsible for differential sensitivity to chemicals across species (Ottinger et al. 2005). In a study examining the toxicity of arsenic and cadmium, the metals were found to cause different toxic interactions depending on the sequence of the exposure (Hochadel and Waalkes 1997). The interactions among contaminants may substantially add, suppress, or multiply the effects of single components.

Ecosystem Biomarkers

Biomarkers are quantitative measures of the biological response of an organism to a chemical and can often be more valuable to environmental assessment than chemical analysis. Biomarkers reflect the concentration of contaminant that is biologically available, giving a true sense of how much of the contaminant is affecting the biota. Biomarker monitoring is often less expensive and more effective than using traditional chemical analysis. The biological responses of organisms to stressors are long-lasting and biomarkers can reveal episodes of contamination that intermittent chemical monitoring would miss (Handy et al. 2003).

Historically, biomarkers have been used to identify contaminated areas and potential stressors (Adams 2003; Adams et al. 2001), but are currently being incorporated into the regulatory framework with varying degrees of success. Scientists offer differing solutions using biomarkers in environmental risk assessment. Adams (Adams 2003; Adams et al. 2001) recommends that an experimental framework of biomarker studies should be developed that applies to each situation and that this general framework should conform to the basic guidelines suggested in the Framework for Ecological Assessment (USEPA 2005a). The generalized field-biomonitoring framework consists of a weight of evidence approach, applying line of evidence at several different levels of biological organization. The appropriate biomarker would then be selected based on the information available (Adams et al. 2001). Adams, et al. (Adams et al. 2001) also recommend the identification of modifying factors that influence the interpretation of biomarker responses to stresses. Handy et al. (Handy et al. 2003) believe that the major drawback of biomarkers is the temporal and spatial variability between biological responses. To overcome the variability, Handy et al. recommend careful selection of reference sites, suites of biomarkers for multivariate analysis, and the introduction of sentinel organisms to calibrate the

temporal shift.

SUMMARY AND RECOMMENDATIONS

In the discussion above, two focus points for were identified for evaluating the capabilities of biomonitoring data – (a) under what circumstances can biomarkers be used to disaggregate disease burden into specific risk factors and (b) when and how can biomarkers be used to infer the source and magnitude of exposure among a set of competing sources and pathways? In the following paragraphs, the case studies above, as well as information in the literature on the availability and use of biomarkers, are used to evaluate the capabilities of biomarkers to address these two focus points for cumulative risk assessments.

The Use of Biomarkers to Disaggregate Disease Burden into Specific Risk Factors

The use of biomarkers to disaggregate disease burden into specific risk factors is an extension of classical epidemiological methods with biomarkers used in place of, or together with, other classification factors. Here the role of biomarkers is to improve resolution in classifying observed disease occurrence by providing factors that are more explicitly causative or explanatory. The greatest opportunity here is learning to integrate markers of exposure with markers of effect and markers of susceptibility.

Some existing studies have demonstrated the clear advantage of biomarkers for sorting out important risk factors, but much remains to be done. For example with lead and mercury, the blood levels serve as biomarkers of exposure that have been important as risk factors for disease. These risk factors are sufficiently reliable that biomonitoring for lead and mercury have shaped prevention strategies, helped susceptible subpopulations, and improved the scientific basis for

health risk estimates. For neurological effects, blood lead measurements have been used both as markers of exposure and markers of effect because the harm to the neurological system depends on the amount of circulating lead in the body. Cotinine has proved useful as a biomarker of exposure to environmental tobacco smoke (ETS) but is not optimum as a biomarker of effect because cotinine is a metabolite of nicotine subject to interindividual variability in measured concentration. To date most efforts to use biomarkers to improve the links among disease patterns and risk factors have been haphazard and opportunistic. For the example substances as well as the broader range of substances having available biomarkers, there is need for a systematic effort to evaluate whether and how links among exposure and other risk factors can be better tracked to disease burden.

Use of Biomarkers to Infer Contributions from Different Sources and Pathways

Most environmental pollutants enter human and ecological receptors from multiple sources and through competing pathways. Effective policies require cumulative risk assessments that not only provide reliable estimates of cumulative intake but also identify the important sources and exposure pathways contributing to this intake. It is common in most risk assessments that this calculation is made in the forward direction—from source to dose. But the increasing availability of population-scale biomonitoring data makes in possible to work in the opposite direction from dose to source. There have been some preliminary efforts to use biomarkers to infer sources and pathways, but such efforts have been limited. There remains the

need for efforts to articulate and evaluate strategies for systematically using biomarkers to infer source and pathway.

The case studies above provide preliminary examples of when and how biomarkers can be used to infer the source and magnitude of exposure among a set of competing sources and pathways. The answer to this question is chemical specific and relates to how well the biomarker matches the characteristics of an "ideal" biomarker – in particular ease of collection and persistence. For example, the dioxins and PCBs, which are persistent in biological organisms, facilitate biomonitoring that has enabled scientists and public health professionals to track population trends and to evaluate progress in reducing exposures. To some extent, biomarkers of dioxin-like substances have also been useful in demonstrating for these compounds the relative importance of global versus regional and local source as well as important contributions through food rather than inhalation pathways. In contrast, biomarkers of a compound that is metabolized relatively quickly provide only limited opportunity for inferring sources or exposure pathways. Biomarkers for OP pesticides are somewhere between the extremes of dioxin-like compounds and rapidly metabolized compounds in providing an opportunity to explore source and pathway contributions. OP pesticides can be measured directly in blood (and possibly in urine) and produce both generic metabolites – dialkyl phosphates – and organophosphate-specific (or near-specific) biomarkers such as TCPy. The use of these three biomarkers in combination provides a better opportunity to disaggregate both source and pathway contributions than is possible for a rapidly metabolized compound. However, little has been done to explore the capabilities and limitations of using multiple biomarkers in combination to infer exposure attributes. Important goals for near term biomarker research must include

systematic efforts across a broad range of chemical substances to determine the reliability of biomarkers to infer the source and exposure pathway in cumulative risk assessments. This may be done most effectively through the simultaneous collection of biomarker data of various types on the same individuals, populations, or ecosystems.

In conclusion, the public health goal of quantifying the burden of disease that is attributable to the cumulative impacts of environmental exposure remains elusive. However, the steady progress in development of biomarkers of exposure, susceptibility, and effect, coupled with emerging technologies for environmental monitoring, offer unprecedented opportunities to examine and prevent cumulative health risks and to redefine approaches to environmental protection.

REFERENCES

Adams SM. 2003. Establishing causality between environmental stressors and effects on aquatic ecosystems. Human and Ecological Risk Assessment 9(1):17-35.

Adams SM, Giesy JP, Tremblay LA, Eason CT. 2001. The use of biomarkers in ecological risk assessment: recommendations from the Christchurch conference on Biomarkers in Ecotoxicology. Biomarkers 6(1):1-6.

Andrae S, Axelson O, Bjorksten B, Fredriksson M, Kjellman NI. 1988. Symptoms of bronchial hyperreactivity and asthma in relation to environmental factors. Archives of Disease in Childhood 63(5):473-478.

Arshad SH, Hide DW. 1992. Effect of environmental factors on the development of allergic disorders in infancy. Journal of Allergy & Clinical Immunology 90(2):235-241.

Barr D, Wang R, Needham LL. 2005. Biologic Monitoring of Exposure to Environmental Chemicals throughout the Life Stages: Requirements and Issues for Consideration for the National Children's Study. Environmental Health Perspectives 113:1083–1091.

Barr DB, Bravo R, Weerasekera G, Caltabiano LM, Whitehead RD, Olsson AO, Caudill SA, Schober, SE, Pirkle JL, Sampson EJ, Jackson RJ, Needham LL. 2004. Concentrations of dialkyl phosphate metabolites of organophosphorus pesticides in the US population. Environmental Health Perspectives 112(2):186-200.

Bartell S, Ponce R, Sanga N, Faustman E. 2000. Human Variability in Mercury Toxicokinetics and Steady State Biomarker Ratios. Environmental Research 84(2):127-132.

Behrendt H, Becker WM, Fritzsche C, Sliwa-Tomczok W, Tomczok J, Friedrichs KH, Ring J. 1997. Air pollution and allergy: experimental studies on modulation of allergen release from pollen by air pollutants. International Archives of Allergy & Immunology 113(1-3):69-74.

Callahan M, Sexton. M. 2006. If “Cumulative Risk Assessment” is the Answer; What is the Question? EPA/630/P-06/XXX. Washington, DC: Risk Assessment Forum.

Chuang H, Schwartz J, Gonzales-Cossio T, Cortez-Lugo M, Palazuelos E, Aro A, Hu H, Hernandez-Avila M. 2001. Interrelations of Lead Levels in Bone, Venous Blood, and Umbilical Cord Blood with Exogenous Lead Exposure through Maternal Plasma Lead in Peripartum Women. Environmental Health Perspectives 109):527–532.

Clarkson T. 1997. The toxicology of mercury. Critical Reviews in Clinical Laboratory Sciences 34(4):369-403.

deFur P, Evans G, Cohen-Hubal E, Kyle A, Morello-Frosch R, Williams D. 2006. Vulnerability as a Function of Individual and Group Resources in Cumulative Risk Assessment. EPA/630/P-06/XXX. Washington, DC: Risk Assessment Forum.

Dejmek J, Selevan SG, Benes I, Solansky I, Sram RJ. 1999. Fetal growth and maternal exposure to particulate matter during pregnancy. Environmental Health Perspectives 107(6):475-480.

Diaz-Sanchez D, Tsien A, Fleming J, Saxon A. 1997. Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human in vivo nasal ragweed-specific IgE and skews cytokine production to a T helper cell 2-type pattern. Journal of Immunology 158(5):2406-2413.

Emberlin J. 1995. Interaction between air pollutants and aeroallergens. Clinical & Experimental Allergy 25 Suppl 3):33-39.

Faust LJ, Jackson R, Ford A, Earnhardt JM, Thompson SD. 2004. Models for management of wildlife populations: lessons from spectacled bears in zoos and grizzly bears in Yellowstone. System Dynamics Review 20(2):163-178.

Fent K. 2004. Ecotoxicological effects at contaminated sites. Toxicology 205:223-240.

Gereda JE, Klinnert MD, Price MR, Leung DY, Liu AH. 2001. Metropolitan home living conditions associated with indoor endotoxin levels. Journal of Allergy & Clinical Immunology 107(5):790-796.

Gereda JE, Leung DY, Thatayatikom A, Streib JE, Price MR, Klinnert MD, Liu, AH. 2000. Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitisation in infants at high risk of asthma.[see comment]. Lancet 355(9216):1680-1683.

Groopman JD, Kensler TW. 2005. Role of metabolism and viruses in aflatoxin-induced liver cancer. Toxicology & Applied Pharmacology 206(2):131-137.

Handy RD, Galloway TS, Depledge MH. 2003. A proposal for the use of biomarkers for the assessment of chronic pollution and in regulatory toxicology. Ecotoxicology 12(1-4):331-343.

Harving H, Dahl R, Molhave L. 1991. Lung function and bronchial reactivity in asthmatics during exposure to volatile organic compounds. American Review of Respiratory Disease 143(4 Pt 1):751-754.

Hochadel JF, Waalkes MP. 1997. Sequence of exposure to cadmium and arsenic determines the extent of toxic effects in male Fischer rats. Toxicology 116(1-3):89-98.

IOM. 2004. Immunization Safety Review: Vaccines and Autism (Medicine Io, ed). Washington DC:National Research Council, Immunization Safety Review Committee, National Academies Press.

Knox RB, Suphioglu C, Taylor P, Desai R, Watson HC, Peng JL, Bursill LA. 1997. Major grass pollen allergen Lol p 1 binds to diesel exhaust particles: implications for asthma and air

pollution. Clinical & Experimental Allergy 27(3):246-251.

Kuzyk ZZ, Burgess NM, Stow JP, Fox GA. 2003. Biological effects of marine PCB contamination on black guillemot nestlings at Saglek, Labrador: liver biomarkers. Ecotoxicology 12(1-4):183-197.

Kyerematen GA, Vesell ES. 1991. Metabolism of Nicotine. Drug Metabolism Reviews 23(1-2.):3-41.

Lange JH. 2002. Airborne exposure and soil levels associated with lead abatement of a steel tank. Toxicology & Industrial Health 18(1):28-38.

Lemly AD. 1997. A teratogenic deformity index for evaluating impacts of selenium on fish populations. Ecotoxicology & Environmental Safety 37(3):259-266.

Lunn JE, Knowelden J, Roe JW. 1970. Patterns of respiratory illness in Sheffield junior schoolchildren. A follow-up study. British Journal of Preventive & Social Medicine 24(4):223-228.

Ma JY, Lin FC, Zhang RZ, Yu WW, Lu NH. 2004. Differential sensitivity of two green algae, Scenedesmus quadricauda and Chlorella vulgaris, to 14 pesticide adjuvants. Ecotoxicology and Environmental Safety 58(1):61-67.

MacIntosh D, Needham L, Hammerstrom K, Ryan PB. 1999. A longitudinal investigation of selected pesticide metabolites in urine. Journal of Exposure Analysis Environmental Epidemiology 9(5):494-501.

Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. 1995. Asthma and wheezing in the first six years of life. The Group Health Medical Associates.[see comment]. New England Journal of Medicine 332(3):133-138.

Menzie C, MacDonnell M, Mumtz M. 2006. Approaches For Assessing Combined Effects From

Multiple Stressors. EPA/630/P-06/XXX. Washington, DC: Risk Assessment Forum.

Metcalf SW, Orloff KG. 2004. Biomarkers of exposure in community settings. Journal of Toxicology & Environmental Health Part A 67(8-10):715-726.

Miller AL. 2001. The etiologies, pathophysiology, and alternative/complementary treatment of asthma. Alternative Medicine Review 6(1):20-47.

Muir DC, Ford CA, Grift NP, Metner DA, Lockhart WL. 1990. Geographic variation of chlorinated hydrocarbons in burbot (Lota lota) from remote lakes and rivers in Canada. Archives of Environmental Contamination & Toxicology 19(4):530-542.

Murray AB, Morrison BJ. 1990. It is children with atopic dermatitis who develop asthma more frequently if the mother smokes. Journal of Allergy & Clinical Immunology 86(5):732-739.

Neas LM, Dockery DW, Ware JH, Spengler JD, Ferris BG, Jr., Speizer FE. 1994. Concentration of indoor particulate matter as a determinant of respiratory health in children.[see comment]. American Journal of Epidemiology 139(11):1088-1099.

Needleman H, Bellinger D. 1991. The health effects of low level exposure to lead. Annual Reviews of Public Health 12):111-140.

Needleman H, Riess J, Tobin M, Biesecker G, Greenhouse J. 1996. Bone lead levels and delinquent behavior. JAMA 275(5):363-369.

NIMH. 2005. What causes ADHD? National Institute of Mental Health. Available: http://www.healthyplace.com/Communities/ADD/nimh/causes.htm [accessed October 16, 2005 2005].

Norris G, YoungPong SN, Koenig JQ, Larson TV, Sheppard L, Stout JW. 1999. An association between fine particles and asthma emergency department visits for children in Seattle.

Environmental Health Perspectives 107(6):489-493.

NRC. 1987. Biological Markers in Environmental Health Research. Environmental Health Perspectives 74:3-9.

---. 2000. Toxicological Effects of Methylmercury Toxicological Effects of Methylmercury (Council CoLSNR, ed):National, Academy Press, Washington, DC.

Ottinger MA, Quinn MJ, Lavoie E, Abdelnabi MA, Thompson N, Hazelton JL, Wu JM, Beavers J, Jaber M. 2005. Consequences of endocrine disrupting chemicals on reproductive endocrine function in birds: Establishing reliable end points of exposure. Domestic Animal Endocrinology 29(2):411-419.

Park JH, Spiegelman DL, Gold DR, Burge HA, Milton DK. 2001. Predictors of airborne endotoxin in the home. Environmental Health Perspectives 109(8):859-864.

Parker S, Schwartz B, Todd J, Pickering L. 2004. Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data." Pediatrics 114):793 –804.

Peterson B, Saxon A. 1996. Global increases in allergic respiratory disease: The possible role of diesel exhaust particles. Annals of Allergy Asthma & Immunology 77(4):263-270.

Platts-Mills TA, Woodfolk JA, Chapman MD, Heymann PW. 1996. Changing concepts of allergic disease: the attempt to keep up with real changes in lifestyles. Journal of Allergy & Clinical Immunology 98(6 Pt 3):S297-306.

Ratcliffe H, Swanson G, Fischer L. 1996. Human exposure to mercury: a critical assessment of the evidence of adverse health effects. Journal of Toxicology and Environmental Health 49(3):221-270.

Romieu I, Meneses F, Ruiz S, Sienra JJ, Huerta J, White MC, Etzel RA. 1996. Effects of air pollution on the respiratory health of asthmatic children living in Mexico City. American

Journal of Respiratory & Critical Care Medicine 154(2 Pt 1):300-307.

Ross G. 2004. The public health implications of polychlorinated biphenyls (PCBs) in the environment. Ecotoxicology and Environmental Safety 59(3):275-291.

Rubbin J, Liu M, Sessoms R, Banerjee S, Banerjee U. 1986. Effects of certain atmospheric pollutants on the soluble amino acides, molecular weight and antigenicity of some airborne pollen grains. Cytobios 46(119-129).

Ruffin J, Liu MY, Sessoms R, Banerjee S, Banerjee UC. 1986. Effects of certain atmospheric pollutants (SO2, NO2 and CO) on the soluble amino acids, molecular weight and antigenicity of some airborne pollen grains. Cytobios 46(185):119-129.

SB702. 2004. Strategies for Establishing an Environmental Health Surveillance System in California A Report of the SB 702 Expert Working Group. Berkeley CA.: The California Policy Research Center.

Schulte P, Mazzuckelli LF. 1991. Validation of biological markers for quantitative risk assessment. Environmental Health Perspectives 90:239-246.

Sexton K, Hattis D. 2006. The Challenge of Assessing Cumulative Exposure and Related Combined Effects from Environmental Mixtures:EPA/630/P-06/XXX. Washington, DC: Risk Assessment Forum.

Tong S, Baghurst P, Sawyer M, Burns J, McMichael A. 1998. Declining Blood Lead Levels and Changes in Cognitive Function During Childhood: The Port Pirie Cohort Study. JAMA 280):1915-1919.

USEPA. 2003. Framework for Cumulative Risk Assessment. Washington, DC: United States Environmental Protection Agency.

---. 2005. Technical Overview of Ecological Risk Assessment. Available:

http://www.epa.gov/oppefed1/ecorisk_ders/ [accessed October 17 2005].

---. 1997. US Environmental Protection Agency Mercury Study Report to Congress, EPA-452/R-97-003.

Ussetti P, Roca J, Agusti AG, Montserrat JM, Rodriguez-Roisin R, Agusti-Vidal A. 1984. Another asthma outbreak in Barcelona: role of oxides of nitrogen. Lancet 1(8369):156.

Wahn U, von Mutius E. 2001. Childhood risk factors for atopy and the importance of early intervention.[see comment]. Journal of Allergy & Clinical Immunology 107(4):567-574.

Ware JH, Ferris BG, Jr., Dockery DW, Spengler JD, Stram DO, Speizer FE. 1986. Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. American Review of Respiratory Disease 133(5.):834-842.

WHO. 1993. Biomarkers and Risk Assessment: Concepts and Principles. Geneva, Switzerland: World Health Organization.

Woods J. 1996. Altered porphyrin metabolism as a biomarker of mercury exposure and toxicity. Canadian Journal of Physiology and Pharmacology 74):210–215.

Xie SC, Yao TD, Kang SC, Xu BQ, Duan KQ, Thompson LG. 2000. Geochemical analyses of a Himalayan snowpit profile: implications for atmospheric pollution and climate. Organic Geochemistry 31(1):15-23.

Table 1. A Comparison of Some Biomarkers to an Ideal Biomarker

Biomarker	Ideal Biomarker K	Cotinine	Blood Lead	Serum Lead	Bone Lead
Associated Exposure	Compound K	Nicotine	Lead	Lead	Lead
Type					
Exposure	Yes	yes	Yes,	Yes	Yes
Effect	Yes	No	Indicative, not definitive	Yes	
Susceptibility	Indicates specific response to compound K	No	No	No	No
Evaluation Characteristics					
Persistence	Yes	No	No	No	Yes
Ease of Collection	Readily Collected	Readily collected	Readily collected	Somewhat Difficult	Difficult
Link to Disease	Direct Between Exposure, Source, and Disease	Unclear. Cotinine is a marker for smoking, but has not been implicated as a causative agent.	Established link between exposure to lead and neurological disease	Established link between exposure to lead and neurological disease	No direct link. Endogenous source of lead from bone may be important
Large Sample	Large percentage of population carries biomarker	Those who smoke or are exposed to ETS.	Yes	Yes	Yes
Broad Spatial Distribution	Occurs across racial and geographic boundaries	Those who smoke or are exposed to ETS.	Yes	Yes	Yes
Appropriate Temporal Occurrence	Occurs over time scales associated with progression of disease	No, short half life for carcinogenesis endpoint	No, recent past exposure	No, recent past exposure	Yes
Sensitivity	Displays dose response	Unclear.	Some indications.	Some indications.	Not known. Few studies.
Parent Compound	Directly measures K	Closely associates with nicotine	Direct measure of lead	Direct measure of lead	Direct measure of lead

Table 2. Example Evaluation for the Outcome - Asthma

	Biomarkers and Health Metrics Associated With Asthma			
Characteristics of an Ideal Biomarker	Immunoglobulin E [IgE] RAST-positivity	T-helper type 2 [Th2] cytokine pattern predominance	Skin Rashes	Food Allergies
Persistence	Good	Good	Irregular	Good
Ease of Collection	Difficult	Difficult	Clinical Evaluation	Clinical Evaluation
Link to Disease	Possibly	Possibly	Possibly	Possibly
Large Sample	Yes	Yes	Unknown	Unknown
Broad Spatial Distribution	Yes	Yes	Unknown	Unknown
Appropriate Temporal Occurrence	Yes	Yes	Possibly	Possibly
Sensitivity	No	No	Possibly	Possibly
Parent Compound	N/A	N/A	N/A	N/A

Figure Legends

Figure 1. Framework for Biomonitoring

Figure 2. Framework Applied to Asthma Case Study

Figure 3. Framework Applied to Neurobehavioral Endpoints Case Study

Figure 4. Framework Applied to Endocrine Disruption Endpoints Case Study. The primary impact here is upon ecological communities.

Figure 1

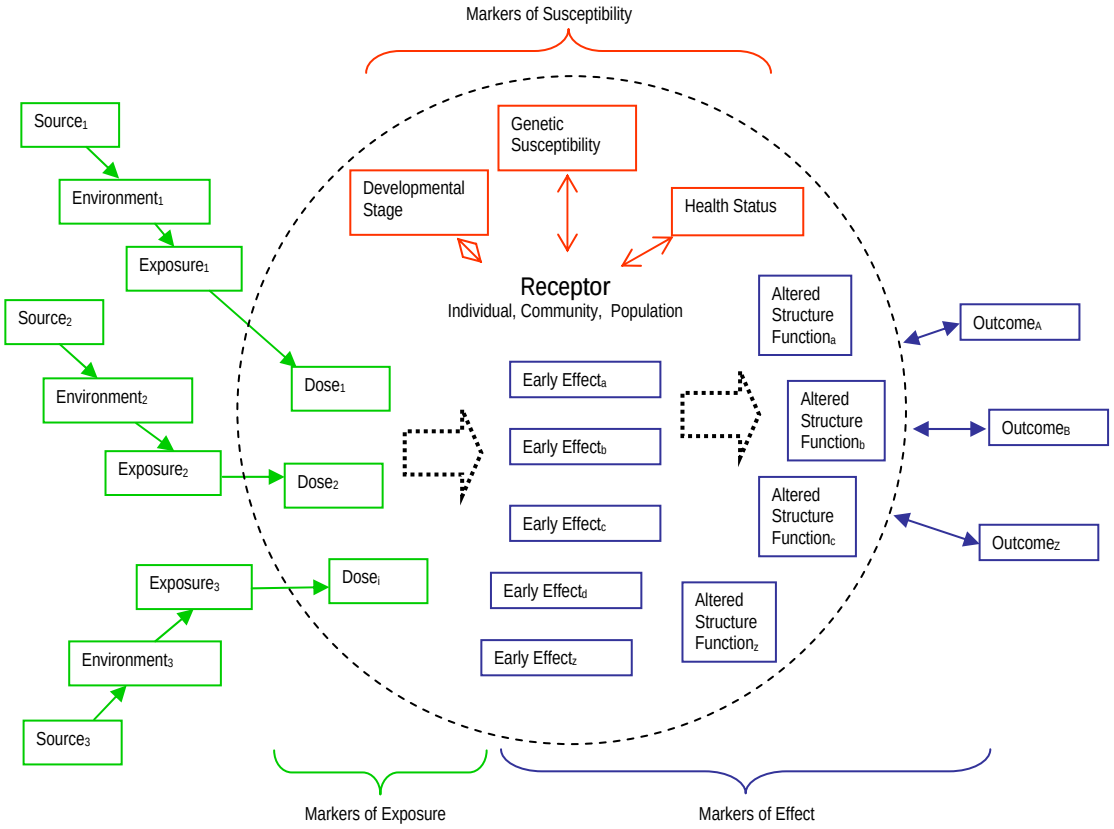

Markers of Susceptibility
Source1
Environment1
Exposure1
Source2
Environment2
Exposure2
Exposure3
Environment3
Source3
Dose1
Dose2
Dosei
Genetic Susceptibility
Developmental Stage
Health Status
Receptor
Individual, Community, Population
Early Effecta
Early Effectb
Early Effectc
Early Effectd
Early Effectz
Altered Structure Functiona
Altered Structure Functionb
Altered Structure Functionc
Altered Structure Functionz
OutcomeA
OutcomeB
OutcomeZ
Markers of Exposure
Markers of Effect

Figure 2

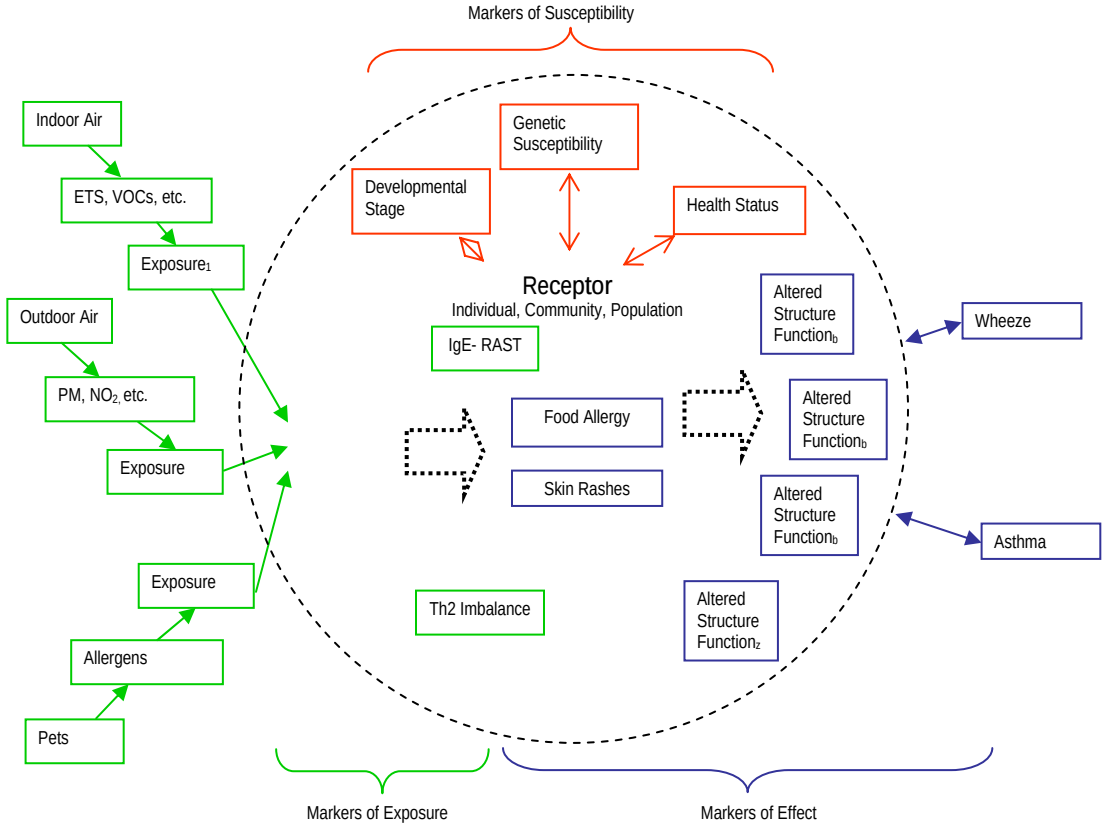

Markers of Susceptibility
Indoor Air
ETS, VOCs, etc.
Exposure1
Outdoor Air
PM, NO2, etc.
Exposure
Exposure
Allergens
Pets
Genetic Susceptibility
Developmental Stage
Health Status
Receptor
Individual, Community, Population
IgE- RAST
Food Allergy
Skin Rashes
Th2 Imbalance
Altered Structure Functionb
Altered Structure Functionb
Altered Structure Functionb
Altered Structure Functionz
Wheeze
Asthma
Markers of Exposure
Markers of Effect

Figure 3

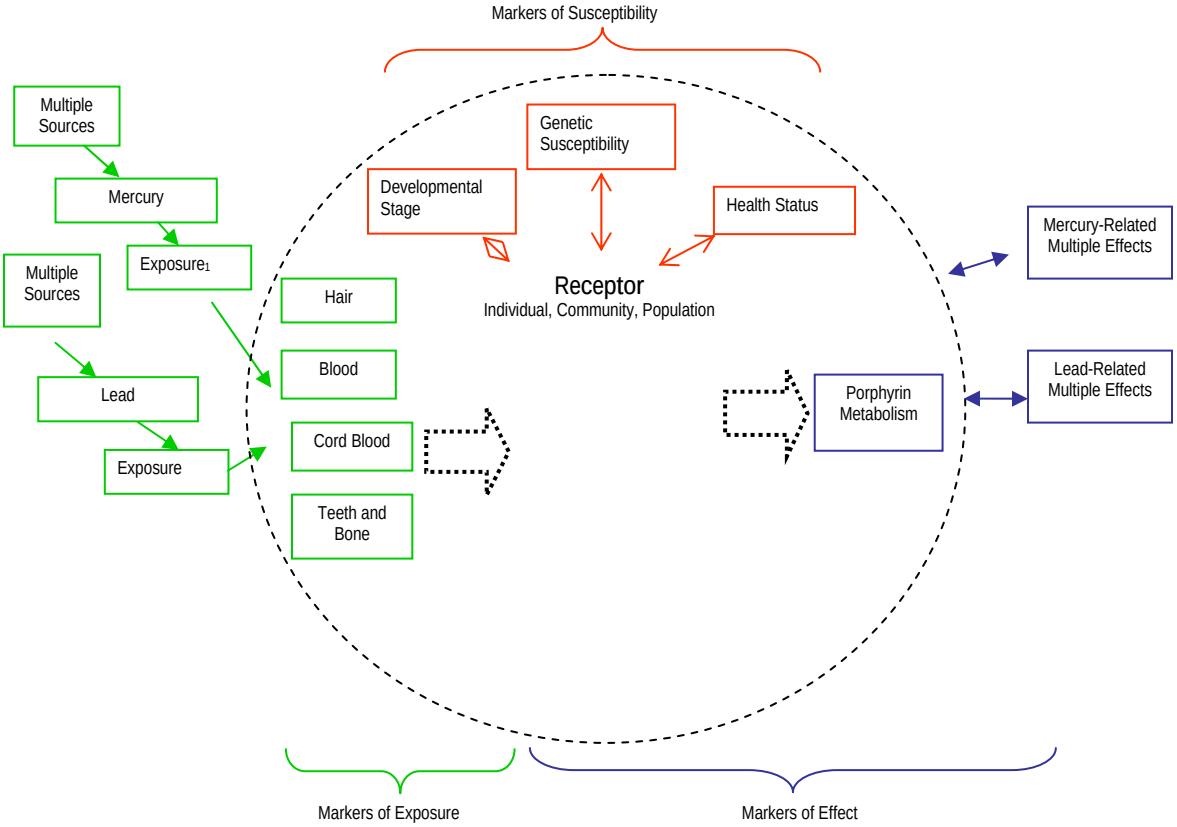
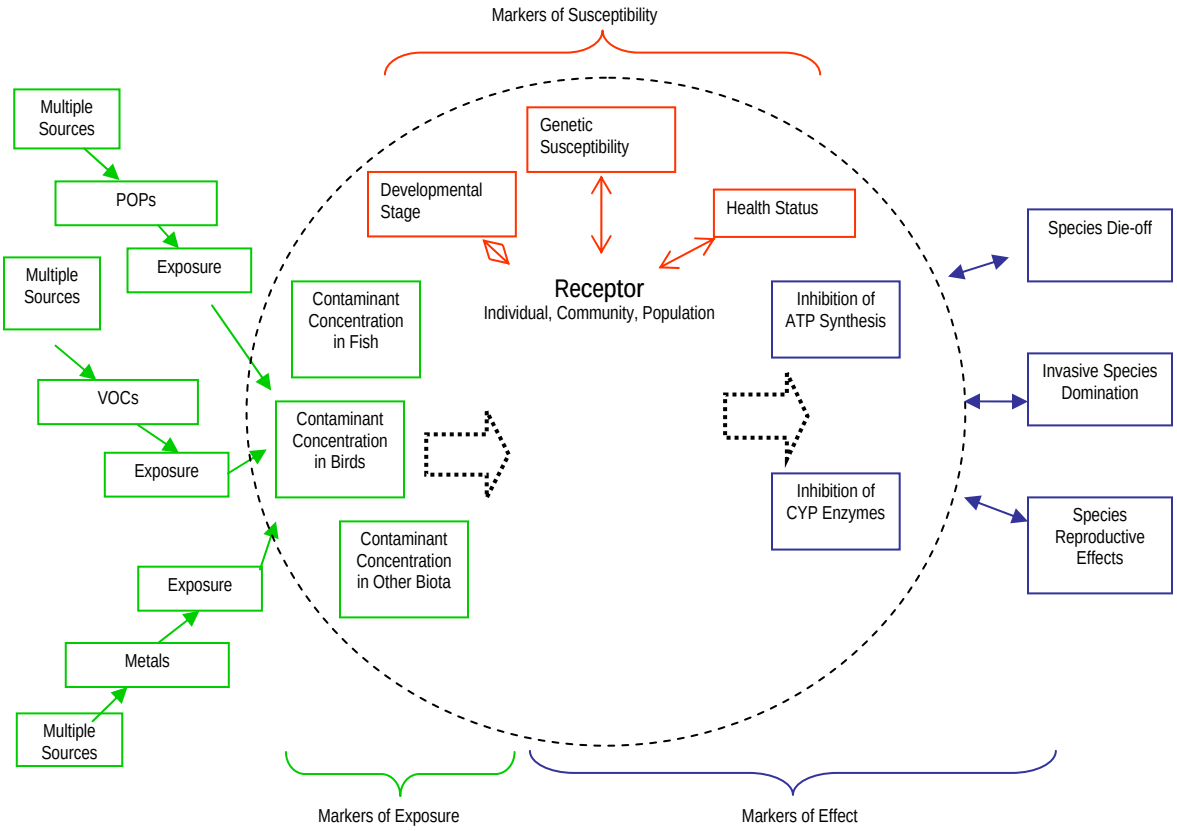

Markers of Susceptibility
Multiple Sources
Mercury
Exposure1
Multiple Sources
Lead
Exposure
Genetic Susceptibility
Developmental Stage
Health Status
Receptor
Individual, Community, Population
Hair
Blood
Cord Blood
Teeth and Bone
Porphyrin Metabolism
Mercury-Related Multiple Effects
Lead-Related Multiple Effects
Markers of Exposure
Markers of Effect

Figure 4


Markers of Susceptibility
Multiple Sources
POPs
Exposure
Multiple Sources
VOCs
Exposure
Exposure
Metals
Multiple Sources
Genetic Susceptibility
Developmental Stage
Health Status
Receptor
Individual, Community, Population
Contaminant Concentration in Fish
Contaminant Concentration in Birds
Contaminant Concentration in Other Biota
Inhibition of ATP Synthesis
Inhibition of CYP Enzymes
Species Die-off
Invasive Species Domination
Species Reproductive Effects
Markers of Exposure
Markers of Effect